REVIEW 10.1111/j.1469-0691.2006.01572.x

# Control of endemic methicillin-resistant *Staphylococcus aureus*—recent advances and future challenges

*S. Harbarth*

Infection Control Program, University of Geneva Hospitals, Geneva, Switzerland

## ABSTRACT

Although the exact burden of disease caused by methicillin-resistant *Staphylococcus aureus* (MRSA) remains largely unknown, most experts agree that MRSA infections are an important clinical and public health problem. Thousands of reports have been published during the last four decades concerning epidemiological and microbiological aspects of MRSA, but uncertainty remains about the best approach to prevent and control this worldwide plague, especially endemic MRSA. Epidemiological methods, e.g., risk scores for targeted screening upon admission, rapid molecular tests and pre-emptive isolation of high-risk patients, new decontamination regimens and restriction of certain antibiotic classes, are all promising approaches that may decrease MRSA cross-transmission; however, further evidence is needed before these strategies can be implemented on a wide scale. Control of community MRSA is an additional challenge for the future, requiring improved surveillance and contact tracing, as well as education and treatment of both infected cases and colonised contacts. This review summarises recent advances and studies that address these issues. Overall, it seems that there is no level of MRSA prevalence for which active control measures are no longer warranted.

**Keywords** Control, cross-infection, epidemiology, MRSA, review, *Staphylococcus aureus*

**Accepted:** 4 July 2006

*Clin Microbiol Infect* 2006; 12: 1154–1162

## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a versatile bacterial pathogen, combining virulence, antibiotic resistance and survival fitness. Clonal spread is facilitated by cross-transmission via the hands of healthcare workers and the selection pressure exerted by broad-spectrum antibiotic treatment. MRSA infections often require systemic antibiotic therapy and are an important healthcare burden, since they increase treatment costs and patient morbidity [1]. Under certain circumstances, MRSA may even contribute to excess mortality. The magnitude of this effect depends on the adequacy of treatment and the patient population studied. In critically-ill patients, microbiologically inadequate therapy for severe MRSA infections may increase the likelihood of death [2]. Conversely, in less severely ill patients, inadequate empirical treatment may not be associated with a greatly increased risk of death after adjusting for independent predictors for mortality [3].

Although the exact burden of disease caused by MRSA remains largely unknown, most experts agree that MRSA infections are an important public health problem that increases the overall burden of infectious disease in a country [4]. This can be best illustrated by the example of the UK, where death certificates are surveyed systematically to determine the proportion of MRSA-related deaths. The most recently published surveillance report revealed that the annual number of death certificates with the mention of MRSA as an underlying cause had increased from 15 to 360 over a decade (Fig. 1) [5].

Although MRSA causes great concern among patients and healthcare professionals, the chances of successful control have been questioned repeatedly for various reasons, including the recent emergence of community MRSA, the increasing

Corresponding author and reprint requests: S. Harbarth, Infection Control Program, The Geneva University Hospitals, 24, rue Micheli-du-Crest, 1211 Geneva 14, Switzerland
E-mail: stephan.harbarth@hcuge.ch

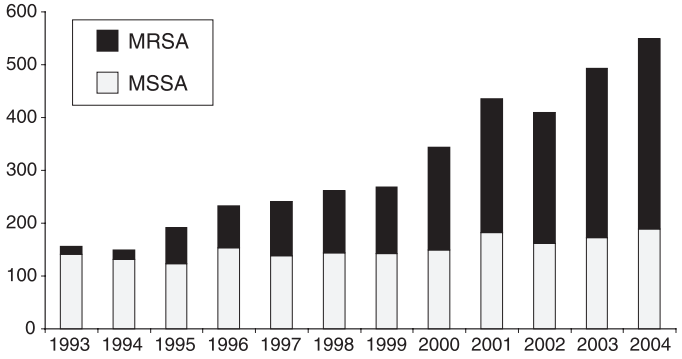


**Fig. 1.** Burden of methicillin-resistant *Staphylococcus aureus* (MRSA) in the UK. Number of death certificates with methicillin-sensitive *S. aureus* (MSSA) or MRSA as the underlying cause, UK (1993–2004). Adapted from [5].

reservoir of nosocomial MRSA, the impossibility of eradicating endemic MRSA, and the significant costs and disruption in patient care associated with active surveillance and control measures [6]. In particular, the most efficient strategy to control endemic MRSA remains controversial [7,8]. This ongoing debate prompts questions concerning evidence-based interventions and innovative approaches that could improve the control of endemic MRSA and reduce its clinical impact. The purpose of the present review is to summarise recent advances and studies that have addressed these issues.

## PREVENTION STRATEGIES FOR ENDEMIC, HEALTHCARE-ASSOCIATED MRSA

Control of endemic MRSA relies on several complementary control strategies that are mentioned frequently in the infection control literature (Fig. 2). First, early detection of asymptomatic MRSA carriers may allow rapid contact isolation and decrease the likelihood of spread. Second, reduction of MRSA carriage with topical treatment and antiseptic body washing, as well as thorough environmental cleaning, may reduce the MRSA reservoir. Third, improved compliance with hand hygiene and standard precautions may decrease transmission. Finally, it has been postulated repeatedly that reduction of antibiotic selection pressure may have a beneficial effect on MRSA acquisition and carriage rates. This review has been structured to consider these basic approaches to the control of MRSA.

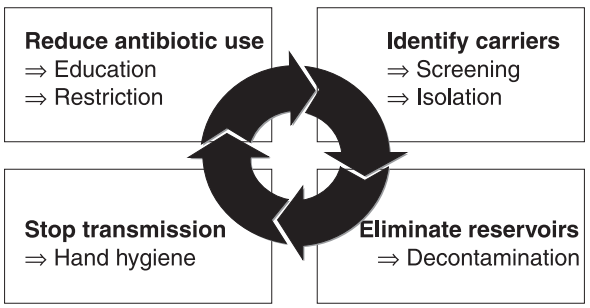


**Fig. 2.** Standard approaches for the control of endemic methicillin-resistant *Staphylococcus aureus*.

## ACTIVE SURVEILLANCE AND ISOLATION

For most patients, MRSA is merely a colonising organism and can only be detected through active screening. Unknown MRSA carriers constitute the main reservoir and source of further spread following hospitalisation. Several recent studies have shown the importance of surveillance cultures of patients in order to prevent MRSA transmission [8-11]. Although the most efficient MRSA screening strategy depends on the local situation, and is still a matter of debate, many affected acute-care hospitals in western and northern Europe have implemented targeted screening policies for patient groups at high risk of MRSA carriage and infection, and apply specific preventive measures (contact isolation) to identified carriers. In an unpublished survey of 68 infectious disease experts from different parts of Europe, 85% indicated that their hospital had implemented some type of patient screening policy.

Recent modelling studies have suggested that a policy of screening newly admitted patients for MRSA, coupled with rapid and effective isolation and treatment, could make a major contribution

to controlling the spread of MRSA [12,13]. Bootsma *et al*. [13] suggested that a full 'search-and-destroy' policy could reduce high MRSA endemicity to a prevalence of <1% within 6–12 years. The most important components of this control strategy involved contact tracing of identified MRSA patients, screening of high-risk patients upon admission, increased adherence to standard hygiene and isolation precautions, and the use of rapid diagnostic tests. Small additional effects were estimated for screening of healthcare workers, use of MRSA decolonisation regimens and closure of wards following identification of large clusters of MRSA patients [13].

In contrast to these modelling studies, Cepeda *et al*. [7] were unable to confirm the efficacy of patient isolation or cohorting in preventing spread of MRSA in two UK intensive care units (ICUs). Possible reasons for the failure of these interventions were as follows: there was a high colonisation pressure upon admission (up to 30% of screened patients were MRSA-positive); only those patients who stayed for >2 days were screened (50% of the overall population); no rapid MRSA screening technique, or pre-emptive isolation while awaiting culture results, was used; only nurse cohorting was performed, without cohorting of other groups of healthcare workers; and hand hygiene compliance was very low (20%).

## PREDICTION OF PREVIOUSLY UNKNOWN MRSA CARRIAGE UPON ADMISSION

Although risk-factors for nosocomial MRSA acquisition have been described in numerous studies, few investigators have developed practical tools to identify previously unknown MRSA carriage upon hospital admission [14,15]. In the study by Troillet *et al*. [14], three patient characteristics (diabetes, antibiotic treatment within the previous 6 months, and exposure to a healthcare facility within the past year) predicted MRSA carriage with a high sensitivity. The study by Lucet *et al*. [15] confirmed the importance of previous healthcare exposure in identifying MRSA carriers upon admission to different ICUs in the Paris region. Two recent studies examining MRSA bacteraemia at the time of hospital admission identified previous hospitalisation, receipt of antibiotics, the presence of indwelling catheters, diabetes mellitus and residence in a nursing home as independent risk-factors [16,17].

In 2003, a prospective, case-controlled, on-admission screening study was conducted with all adult inpatients admitted to Geneva University Hospitals in order to determine the prevalence and risk profile of patients with previously unknown carriage of MRSA upon hospital admission [18]. Multivariate conditional logistic regression for datasets, matched 1:4, was performed in order to identify the risk profile of newly identified MRSA carriers. Overall, 399 of 12 072 screened admissions (a prevalence of 3.3%) were MRSA-positive. MRSA carriage was newly identified in 204 individuals (a prevalence of 1.7%). Nine independent risk-factors were identified for MRSA carriage upon admission (adjusted OR): male gender (1.9); age >75 years (2.0); receipt of fluoroquinolones (2.7), cephalosporins (2.1) or carbapenems (3.2) during the previous 6 months; hospitalisation (1.9) or intravenous therapy (1.7) during the previous 12 months; urinary catheter upon admission (2.0); and intra-hospital transfer (2.4).

Based on the results of a simplified multivariate analysis ($n$ = 594), and by adding points assigned to four easily retrievable variables (age >80 years, hospitalisation within the previous 12 months, antibiotic use within the previous 6 months, and the presence of a urinary catheter upon admission), a practical risk score was calculated for patients admitted to the acute-care sector [18]. The probability of MRSA carriage was 8% in patients with 0 points, 18% in those with 1 point, 31% in those with 2 points, and 57% in those with ≥3 points (Fig. 3). In the presence of any of these risk-factors, this model

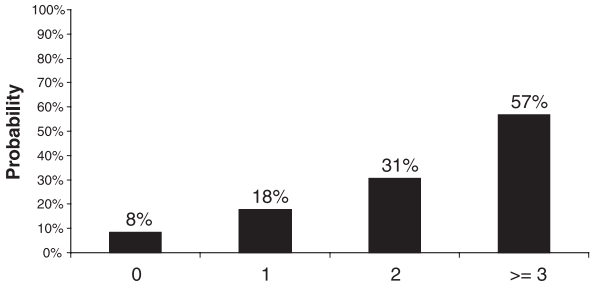


**Fig. 3.** Risk score model to identify previously unknown carriage of methicillin-resistant *Staphylococcus aureus* upon admission to the acute-care sector of Geneva University Hospitals (2003). Adapted from [18].

would have identified 84% of patients (100/119), but would have required the screening of 64% of the patients admitted. An on-admission study from the USA validated this risk index, demonstrating almost identical results (sensitivity, 84%; number of patients to be screened, 65%) [19]. Both studies concluded that the prevalence of previously unknown MRSA carriers upon admission is high in settings with endemic MRSA, and that applying a risk score to newly admitted patients with an intermediate or high probability of MRSA carriage could form part of a more effective control strategy.

For the geriatric setting, an independent risk index was calculated and validated with a separate dataset generated during 2001 [20]. The prevalence of MRSA carriage upon admission to the geriatric hospital in Geneva increased from 7.3% (53/724 patients) in 2001 to 8.7% (78/897) in 2003, with a corresponding prevalence of unknown MRSA carriers of 4.6% and 5.8%, respectively. Three variables were associated independently with previously unknown MRSA carriage: recent antibiotic treatment (adjusted OR 2.3); intra-hospital transfer (2.5); and hospitalisation during the past 2 years (2.7). In the validation cohort, the probability of MRSA carriage increased across risk scores: 0 points, 4% prevalence (6/146); 1 point, 15% (21/136); and ≥2 points, 31% (21/68; $p < 0.001$). This risk score showed good discrimination and calibration in both groups.

## RAPID SCREENING WITH MOLECULAR TESTS

Application of rapid MRSA screening tools may improve patient outcomes by decreasing MRSA transmission and infection rates, and by directing the choice of antibiotic agents (e.g., vancomycin) for antibiotic prophylaxis and treatment. Previous studies concerning rapid MRSA screening tests did not examine their effect on infection rates, and assessed only the time of specimen processing, without taking into account transport of specimens and the delay between admission and screening [21,22]. Therefore, an interventional cohort study was conducted to assess whether a new molecular technique enabling early detection of MRSA carriage can decrease the time between ICU admission and identification of previously unknown MRSA carriers, and whether this new method has an effect on ICU-acquired MRSA infections [23]. All patients admitted for >24 h to two ICUs were screened systematically upon admission by multiplex immunocapture-coupled PCR [24]. This test allows quick diagnosis of MRSA carriage through detection of the *mecA* gene (in *S. aureus* and *Staphylococcus epidermidis*). Median time to notification decreased from 87 h to 21 h in the surgical ICU ($p < 0.05$), and from 106 h to 23 h in the medical ICU ($p < 0.05$). No effect on MRSA prevalence was observed in the surgical ICU, although a large number of unnecessary pre-emptive isolation-days could be saved by using the rapid test. A substantial decrease in MRSA infections was seen in the medical ICU after increasing the compliance with on-admission screening and implementation of a strategy linking the rapid test to pre-emptive isolation and cohorting of MRSA patients [23] (Fig. 4).

## PATIENT DECOLONISATION

Carriage of MRSA is an important risk-factor for subsequent infection, and facilitates cross-transmission. Based on these assumptions, several intervention studies have been performed with the aim of reducing the rates of MRSA infection by eradicating MRSA carriage. In particular, mupirocin nasal ointment has been used to eradicate carriage because of its effectiveness, safety and relatively low cost [25]. Although some data suggest that mupirocin is effective in reducing nasal carriage of *S. aureus*, a recent systematic review concluded that there is insufficient evidence to support the use of topical or systemic antimicrobial therapy for eradicating extra-nasal MRSA carriage, except in well-defined outbreak settings [26]. Results from a randomised, placebo-controlled trial performed at our institution did not support the hypothesis that routine use of topical intra-nasal mupirocin for prevention of MRSA infections is warranted for all MRSA carriers [27], and also revealed that mupirocin should not be used in patients presenting with open sores or medical devices [27,28].

The exact role of stool colonisation by MRSA is still a matter of debate. Two recent studies have suggested that MRSA stool carriage is an important reservoir and that topical decontamination with oral vancomycin may have a beneficial effect [29,30]. Clearly, more controlled

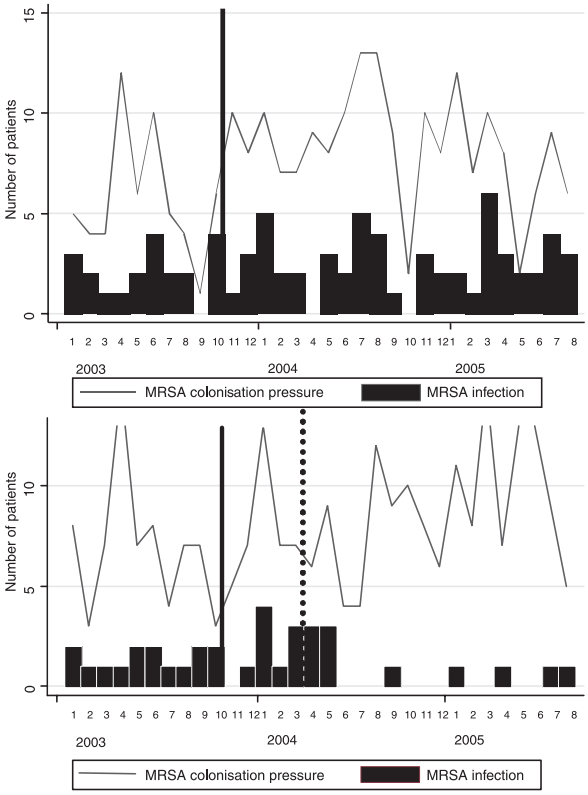


**Fig. 4.** Previously known carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) upon admission vs. intensive care unit (ICU)-acquired MRSA infection. Shown are the number of patients with previously known MRSA carriage upon admission (MRSA colonisation pressure) and the number of patients with ICU-acquired MRSA infections (surgical and medical ICUs; Geneva University Hospitals; January 2003 to August 2005). Lower panel, medical ICU: The vertical line indicates the initiation of rapid on-admission screening in November 2003. The dashed vertical line indicates the initiation of pre-emptive isolation for all patients in April 2004. Upper panel, surgical ICU: The vertical line indicates the initiation of rapid MRSA screening upon admission and the extension of pre-emptive isolation in November 2003. Adapted from [23].

studies are needed before this practice is widely adopted.

Although many different topical skin decontamination regimens are in use, the evidence base for this practice remains weak. An intervention study from the USA has shown that the application of a chlorhexidine-based skin decontamination regimen for critically-ill patients resulted in decreased acquisition of MRSA, as well as decreased skin and environmental contamination with vancomycin-resistant enterococci [31]. This procedure also had an effect on MRSA infection rates (M. Hayden, personal communication).

## ENVIRONMENTAL CONTROL

For more than two decades, infection control focused on patients, rather than the patients' environment, as the most important source of nosocomial infection. This approach was based on studies that failed to find reductions in the rates of nosocomial infection after hospital units were moved into new, clean accommodation [32]. However, there is a growing body of literature emphasising that MRSA is ubiquitous in the hospital environment of MRSA patients, and that it can be cross-transmitted easily on the hands of healthcare workers [33]. Therefore, appropriate cleaning and disinfection procedures are essential to decrease the microbial burden in the close patient environment and to minimise the likelihood of MRSA cross-infection. Recent provisional data (16th European Congress for Clinical Microbiology and Infectious Diseases, abstracts P1333 and P1336) suggest that thorough patient and environmental decontamination regimens may help to decrease MRSA acquisition when used in combination with other control measures.

## HAND HYGIENE

MRSA mostly spreads from patient to patient via the transiently colonised hands of healthcare workers during patient contact or after handling contaminated materials. Strict compliance with standard precautions, e.g., hand disinfection, could prevent most cases of cross-transmission without any need for recognition of individual MRSA carriers. Unfortunately, it has been shown that the compliance of healthcare workers with hand hygiene recommendations is poor [34]. Alcohol-based antiseptic agents at the bedside have great potential for increasing compliance, as they allow fast hand hygiene procedures during patient care, achieve rapid microbial killing, and may even improve the skin condition of the hands of healthcare workers [35].

Several studies have shown that promotion of alcohol-based hand rinses can improve compliance and save money by reducing episodes of cross-infection [36,37]. A report from Australia has shown that improved MRSA control can be achieved through promotion of alcohol-based

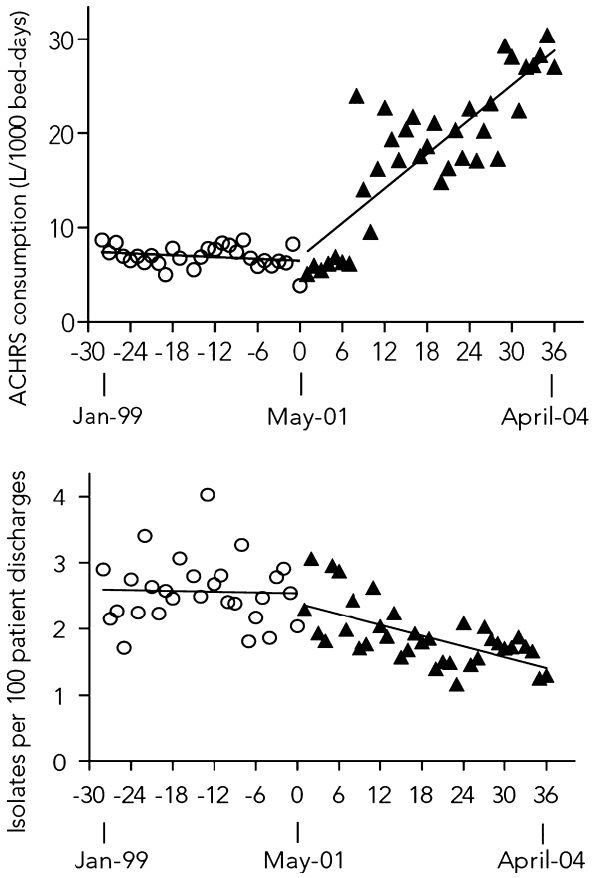


**Fig. 5.** Use of alcohol-based hand rubs (ACHRS) (upper panel) and the frequency of clinical methicillin-resistant *Staphylococcus aureus* isolates (lower panel); Austin Health (840-bed University of Melbourne teaching hospital), 1999–2004. Adapted with permission from [38].

hand hygiene (Fig. 5), which does not need to be costly [38]. Large-scale public health interventions, e.g., the recently launched WHO campaign 'Clean care is safer care', may contribute to a decrease in MRSA infection rates [39].

## ANTIBIOTIC RESTRICTION

Antibiotic selection pressure greatly facilitates acquisition and persistent colonisation of MRSA by decreasing colonisation resistance and eradicating competing susceptible flora [40]. Fluoroquinolones, in particular, tend to increase the occurrence and persistence of multiresistant staphylococci [41]. In an outbreak report from Germany, thorough investigation of multiple risk-factors showed that previous fluoroquinolone exposure was an independent risk-factor for carriage of MRSA [42]. Moreover, in a prospective cohort study, fluoroquinolone exposure was found to predict prolonged MRSA carriage and to decrease the likelihood of MRSA eradication [28].

Despite these observational studies, the effect of antibiotic control policies in the prevention of nosocomial MRSA acquisition and cross-infection remains uncertain. A systematic review has highlighted the weakness of much of the evidence concerning this issue [43], since only one study was considered adequate in assessing the effect of an antibiotic control strategy on nosocomial MRSA transmission. In that study, no effect on MRSA occurrence was observed during a 7-year period [44]. However, data from two recently published intervention studies in France and the USA suggest that restriction of fluoroquinolone use may decrease MRSA rates [45,46]. Clearly, other well-designed investigations are needed to determine whether reductions in overuse of antimicrobial agents and improvements in antimicrobial selection have a favourable effect on MRSA rates.

## NEW CHALLENGES AHEAD: COMMUNITY MRSA

The scope of staphylococcal antibiotic resistance is currently extending to more clinical settings and to new patient populations. While antibiotic-resistant *S. aureus* was once thought to be confined to large hospitals, community outbreaks of MRSA are now occurring in individuals without traditional risk-factors for carriage of MRSA. Although outpatients with a history of intravenous drug use, nursing home residency or recent hospitalisation appear to have a heightened risk for MRSA carriage [18,47], a significant minority of patients admitted with MRSA carriage do not have such identifiable risk-factors.

The prevalence of community-associated (CA) MRSA carriage in Europe remains largely unknown, since few systematic studies have assessed its epidemiology [48]. Determining the epidemiology of CA-MRSA could help in the development of control measures and in guiding clinicians in the identification of patients at high risk of CA-MRSA. Therefore, based on the previously described on-admission screening study conducted in 2003 [18], an observational study was conducted to determine the prevalence of CA-MRSA upon hospital admission to our insti-

tution and to examine the characteristics of patients carrying CA-MRSA [49]. The study revealed: (i) a low prevalence of CA-MRSA upon hospital admission (9/10 000 admissions); (ii) a reservoir of asymptomatic carriers of exotoxin-containing CA-MRSA strains; (iii) no readily modifiable risk-factor for CA-MRSA acquisition; and (iv) a high degree of molecular diversity of CA-MRSA in the study population [49].

Since 2002, a CA-MRSA surveillance system has been established in Geneva in order to ensure adequate case investigation and contact tracing, to estimate incidence and transmission patterns, and to develop targeted prevention strategies. The medical community and the two main microbiology laboratories participate actively on a voluntary basis in the surveillance system [50]. Between January 2002 and December 2004, 58 cases of CA-MRSA were reported; 41 cases (71%) were infected and 17 (29%) were colonised. Abscesses and furunculosis were the most common clinical presentations. Seven cases were temporary residents who lived abroad, and 38 had travelled abroad in the preceding 12 months. A total of 26 cases could be grouped into 13 distinct transmission clusters [50].

## NOSOCOMIAL TRANSMISSION OF CA-MRSA

CA-MRSA can spread easily within the healthcare setting, especially in neonatal and paediatric wards [51]. Several recent reports have described measures to control nosocomial outbreaks of CA-MRSA in neonatal units [52]. In a series of eight post-partum women who were involved in a nosocomial cluster of cases of Panton–Valentine leukocidin-producing CA-MRSA causing mastitis, cellulitis and surgical site infection, the outbreak was terminated by screening and contact isolation [53]. Another outbreak in a nursery in Norway, caused by an unusual MRSA strain associated with pustulosis in seven neonates, was halted by stringent preventive measures, including closure of the unit and an increased staffing level [54].

The identification of a cluster of seven premature neonates colonised with MRSA between 20 June and 29 July 2000 in Geneva prompted an epidemiological investigation [55]. This revealed the first documented outbreak of Panton–Valentine leukocidin-producing CA-MRSA (ST5-MRSA-IV) in a European neonatal ICU, which was paralleled by a small cluster of MRSA cases caused by an endemic nosocomial strain (ST228-MRSA-I). Active surveillance, contact isolation and detailed molecular analysis helped to elucidate and terminate this outbreak after a period of 6 weeks. One infant involved in the summer 2000 outbreak had persistent CA-MRSA carriage, resulting in skin infection in a sibling 4 years after the initial outbreak [55].

## CONCLUSIONS

The exact burden of disease caused by MRSA remains largely unknown, and there is still contradictory evidence with respect to key questions concerning the most cost-effective methods for control of endemic MRSA. Several well-conducted studies from France, Germany, the UK and the USA have illustrated this dilemma. Use of epidemiological methods, e.g., risk scores for targeted on-admission screening, rapid molecular tests and pre-emptive isolation of high-risk patients, new decontamination regimens and restriction of certain antibiotic classes, provide promising approaches towards decreasing MRSA cross-transmission; however, further evidence is needed to implement these strategies on a wide scale. Control of community MRSA infections is an additional challenge for the future, requiring improved surveillance, contact tracing, education, and treatment of both infected cases and colonised contacts. Whatever the final outcome of the ongoing debate concerning the most efficient way to control endemic MRSA infections, health authorities and policy-makers would be well-advised to put stringent efforts and funds into their control efforts. MRSA is a concern for everyone, not just hospital epidemiologists and a few opinion leaders [56].

## ACKNOWLEDGEMENTS

This review is based on an ESCMID Award Lecture presented at the 16th European Congress of Clinical Microbiology and Infectious Diseases (Nice, 2006). The author wishes to thank his collaborators in the Infection Control Team, the Clinical Microbiology Laboratory, the Genomics Laboratory and the Division of Infectious Diseases. Without their commitment and help, this work would not have been possible. Finally, D. Pittet, M. Samore, D. Goldmann, Y. Carmeli and J. Schrenzel are thanked for inspiration, support and scientific collaboration. This work was supported, in part, by grants from the Geneva University Hospitals (CI 70897) and the Swiss National Science Foundation (grant 404940-106294).

## REFERENCES


1. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 2005; **26**: 166–174.
2. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003; **115**: 529–535.
3. Kim SH, Park WB, Lee CS *et al.* Outcome of inappropriate empirical antibiotic therapy in patients with *Staphylococcus aureus* bacteraemia: analytical strategy using propensity scores. *Clin Microbiol Infect* 2006; **12**: 13–21.
4. Gould IM. The clinical significance of methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 2005; **61**: 277–282.
5. Anonymous. Report: deaths involving MRSA: England and Wales, 2000–2004. *Health Stat Q* 2006; **29**: 63–68.
6. Marshall C, Wesselingh S, McDonald M, Spelman D. Control of endemic MRSA—what is the evidence? A personal view. *J Hosp Infect* 2004; **56**: 253–268.
7. Cepeda JA, Whitehouse T, Cooper B *et al.* Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study. *Lancet* 2005; **365**: 295–304.
8. Wernitz MH, Swidsinski S, Weist K *et al.* Effectiveness of a hospital-wide selective screening programme for methicillin-resistant *Staphylococcus aureus* (MRSA) carriers at hospital admission to prevent hospital-acquired MRSA infections. *Clin Microbiol Infect* 2005; **11**: 457–465.
9. Tomic V, Svetina Sorli P, Trinkaus D, Sorli J, Widmer AF, Trampuz A. Comprehensive strategy to prevent nosocomial spread of methicillin-resistant *Staphylococcus aureus* in a highly endemic setting. *Arch Intern Med* 2004; **164**: 2038–2043.
10. Schelenz S, Tucker D, Georgeu C *et al.* Significant reduction of endemic MRSA acquisition and infection in cardiothoracic patients by means of an enhanced targeted infection control programme. *J Hosp Infect* 2005; **60**: 104–110.
11. Lucet JC, Paoletti X, Lolom I *et al.* Successful long-term program for controlling methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intens Care Med* 2005; **31**: 1051–1057.
12. Cooper BS, Medley GF, Stone SP *et al.* Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: stealth dynamics and control catastrophes. *Proc Natl Acad Sci USA* 2004; **101**: 10223–10228.
13. Bootsma MC, Diekmann O, Bonten MJ. Controlling methicillin-resistant *Staphylococcus aureus*: quantifying the effects of interventions and rapid diagnostic testing. *Proc Natl Acad Sci USA* 2006; **103**: 5620–5625.
14. Troillet N, Carmeli Y, Samore MH *et al.* Carriage of methicillin-resistant *Staphylococcus aureus* at hospital admission. *Infect Control Hosp Epidemiol* 1998; **19**: 181–185.
15. Lucet JC, Chevret S, Durand-Zaleski I, Chastang C, Regnier B. Prevalence and risk factors for carriage of methicillin-resistant *Staphylococcus aureus* at admission to the intensive care unit: results of a multicenter study. *Arch Intern Med* 2003; **163**: 181–188.
16. Rezende NA, Blumberg HM, Metzger BS, Larsen NM, Ray SM, McGowan JE. Risk factors for methicillin-resistance among patients with *Staphylococcus aureus* bacteremia at the time of hospital admission. *Am J Med Sci* 2002; **323**: 117–123.
17. Tacconelli E, Venkataraman L, De Girolami PC, D'Agata EM. Methicillin-resistant *Staphylococcus aureus* bacteraemia diagnosed at hospital admission: distinguishing between community-acquired versus healthcare-associated strains. *J Antimicrob Chemother* 2004; **53**: 474–479.
18. Harbarth S, Sax H, Fankhauser-Rodriguez C, Schrenzel J, Agostinho A, Pittet D. Evaluating the probability of previously unknown carriage of MRSA at hospital admission. *Am J Med* 2006; **119**: 275.e15–e23.
19. Furuno JP, McGregor JC, Harris AD *et al.* Identifying groups at high risk for carriage of antibiotic-resistant bacteria. *Arch Intern Med* 2006; **166**: 580–585.
20. Sax H, Harbarth S, Gavazzi G *et al.* Prevalence and prediction of previously unknown MRSA carriage on admission to a geriatric hospital. *Age Ageing* 2005; **34**: 456–462.
21. Warren DK, Liao RS, Merz LR, Eveland M, Dunne WM. Detection of methicillin-resistant *Staphylococcus aureus* directly from nasal swab specimens by a real-time PCR assay. *J Clin Microbiol* 2004; **42**: 5578–5581.
22. Huletsky A, Lebel P, Picard FJ *et al.* Identification of methicillin-resistant *Staphylococcus aureus* carriage in less than 1 hour during a hospital surveillance program. *Clin Infect Dis* 2005; **40**: 976–981.
23. Harbarth S, Masuet-Aumatell C, Schrenzel J *et al.* Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant *Staphylococcus aureus* in critical care: an interventional cohort study. *Crit Care* 2006; **10**: R25.
24. Francois P, Pittet D, Bento M *et al.* Rapid detection of methicillin-resistant *Staphylococcus aureus* directly from sterile or nonsterile clinical samples by a new molecular assay. *J Clin Microbiol* 2003; **41**: 254–260.
25. Laupland KB, Conly JM. Treatment of *Staphylococcus aureus* colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. *Clin Infect Dis* 2003; **37**: 933–938.
26. Loeb M, Main C, Walker-Dilks C, Eady A. Antimicrobial drugs for treating methicillin-resistant *Staphylococcus aureus* colonization. *Cochrane Database Syst Rev* 2003; CD003340.
27. Harbarth S, Dharan S, Liassine N, Herrault P, Auckenthaler R, Pittet D. Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1999; **43**: 1412–1416.
28. Harbarth S, Liassine N, Dharan S, Herrault P, Auckenthaler R, Pittet D. Risk factors for persistent carriage of methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2000; **31**: 1380–1385.
29. Boyce JM, Havill NL, Maria B. Frequency and possible infection control implications of gastrointestinal colonization with methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol* 2005; **43**: 5992–5995.
30. Thorburn K, Taylor N, Saladi SM, van Saene HK. Use of surveillance cultures and enteral vancomycin to control methicillin-resistant *Staphylococcus aureus* in a paediatric intensive care unit. *Clin Microbiol Infect* 2006; **12**: 35–42.
31. Vernon MO, Hayden MK, Trick WE, Hayes RA, Blom DW, Weinstein RA. Chlorhexidine gluconate to cleanse patients

in a medical intensive care unit: the effectiveness of source control to reduce the bioburden of vancomycin-resistant enterococci. *Arch Intern Med* 2006; **166**: 306–312.
32. Huebner J, Frank U, Kappstein I *et al.* Influence of architectural design on nosocomial infections in intensive care units—a prospective 2-year analysis. *Intens Care Med* 1989; **15**: 179–183.
33. Boyce JM, Potter-Bynoe G, Chenevert C, King T. Environmental contamination due to methicillin-resistant *Staphylococcus aureus*: possible infection control implications. *Infect Control Hosp Epidemiol* 1997; **18**: 622–627.
34. Pittet D, Boyce JM. Hand hygiene and patient care: pursuing the Semmelweis legacy. *Lancet Infect Dis* 2001; **1**: 9–20.
35. Harbarth S. Handwashing—the Semmelweis lesson misunderstood? *Clin Infect Dis* 2000; **30**: 990–991.
36. Harbarth S, Pittet D, Grady L *et al.* Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. *Pediatr Infect Dis J* 2002; **21**: 489–495.
37. Pittet D, Sax H, Hugonnet S, Harbarth S. Cost implications of successful hand hygiene promotion. *Infect Control Hosp Epidemiol* 2004; **25**: 264–266.
38. Johnson PD, Martin R, Burrell LJ *et al.* Efficacy of an alcohol/chlorhexidine hand hygiene program in a hospital with high rates of nosocomial MRSA infection. *Med J Aust* 2005; **183**: 509–514.
39. Pittet D, Donaldson L. Clean care is safer care: a worldwide priority. *Lancet* 2005; **366**: 1246–1247.
40. Muller AA, Mauny F, Bertin M *et al.* Relationship between spread of methicillin-resistant *Staphylococcus aureus* and antimicrobial use in a French university hospital. *Clin Infect Dis* 2003; **36**: 971–978.
41. Weber SG, Gold HS, Hooper DC, Karchmer AW, Carmeli Y. Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized patients. *Emerg Infect Dis* 2003; **9**: 1415–1422.
42. Dziekan G, Hahn A, Thune K *et al.* Methicillin-resistant *Staphylococcus aureus* in a teaching hospital: investigation of nosocomial transmission using a matched case-control study. *J Hosp Infect* 2000; **46**: 263–270.
43. Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: a systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. *J Antimicrob Chemother* 2003; **52**: 764–771.
44. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003; **24**: 699–706.
45. Charbonneau P, Parienti JJ, Thibon P *et al.* Fluoroquinolone use and methicillin-resistant *Staphylococcus aureus* isolation rates in hospitalized patients: a quasi experimental study. *Clin Infect Dis* 2006; **42**: 778–784.
46. Madaras-Kelly KJ, Remington RE, Lewis PG, Stevens DL. Evaluation of an intervention designed to decrease the rate of nosocomial methicillin-resistant *Staphylococcus aureus* infection by encouraging decreased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2006; **27**: 155–169.
47. Fleisch F, Oechslin EC, Gujer AR *et al.* Transregional spread of a single clone of methicillin-resistant *Staphylococcus aureus* between groups of drug users in Switzerland. *Infection* 2005; **33**: 273–277.
48. Grundmann H, Tami A, Hori S, Halwani M, Slack R. Nottingham *Staphylococcus aureus* population study: prevalence of MRSA among elderly people in the community. *BMJ* 2002; **324**: 1365–1366.
49. Harbarth S, Francois P, Shrenzel J *et al.* Community-associated methicillin-resistant *Staphylococcus aureus*, Switzerland. *Emerg Infect Dis* 2005; **11**: 962–965.
50. Aramburu C, Harbarth S, Liassine N *et al.* Community-acquired methicillin-resistant *Staphylococcus aureus* in Switzerland: first surveillance report. *Euro Surveill* 2006; **11**: 42–43.
51. Bratu S, Eramo A, Kopec R *et al.* Community-associated methicillin-resistant *Staphylococcus aureus* in hospital nursery and maternity units. *Emerg Infect Dis* 2005; **11**: 808–813.
52. Regev-Yochay G, Rubinstein E, Barzilai A *et al.* Methicillin-resistant *Staphylococcus aureus* in neonatal intensive care unit. *Emerg Infect Dis* 2005; **11**: 453–456.
53. Saiman L, O'Keefe M, Graham PL *et al.* Hospital transmission of community-acquired methicillin-resistant *Staphylococcus aureus* among postpartum women. *Clin Infect Dis* 2003; **37**: 1313–1319.
54. Andersen BM, Lindemann R, Bergh K *et al.* Spread of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive unit associated with understaffing, overcrowding and mixing of patients. *J Hosp Infect* 2002; **50**: 18–24.
55. Sax H, Posfay-Barbe K, Harbarth S *et al.* Control of a cluster of community-associated, methicillin-resistant *Staphylococcus aureus* in neonatology. *J Hosp Infect* 2006; **63**: 93–100.
56. Harbarth S, Pittet D. Control of nosocomial methicillin-resistant *Staphylococcus aureus*: where shall we send our hospital director next time? *Infect Control Hosp Epidemiol* 2003; **24**: 314–316.